Introduction
ADHD is typically diagnosed in young children and is estimated to affect millions of children throughout the world. It has been found to occur in "virtually every country in which it has been investigated." ADHD has in fact been investigated in several countries, so it is not an 'only in America' disorder. Although figures relating to prevalence vary in the literature, it is generally considered to affect between 2% and 9% of children. The average figure given is 5%, an incidence that is also described as "approximately one child in every classroom." There is a higher incidence of the disorder in boys, who are generally considered to outnumber girls at about 3:1. The age of onset can vary, but the behavior patterns that characterize ADHD usually start at between three and five years of age.

History of ADHD
Hippocrates was said to have described a disorder like ADHD in which the patient had quickened responses to sensory experience, and then quickly moved on to the next impression.

The German physician Hoffman, in the early 1860s wrote a poem about a hyperactive child called 'Fidgety Phil.' Part of it reads: "Phil, stop acting like a worm, the table is no place to squirm. Thus speaks the father to his son, severely say it, not in fun. Mother frowns and looks around, although he doesn't make a sound. But Phillip will not take advice, he'll have his way at any price. He turns and churns, he wriggles and jiggles here and there on the chair. Phil, these twists I cannot bear."

ADHD was also described almost a century ago by Still (the famous physician) in lectures presented to the Royal College of Physicians in 1902. Still described children in his clinical practice who were often resistant to discipline and showed little "inhibitory volition." Most were also overactive and demonstrated impaired attention. In the language of the time these symptoms were thought to be due to defective moral control. As understanding of the disorder increased, and the diagnostic criteria were refined, the names of the disorder changed. Over the years the condition has been labelled, in turn, "minimal brain damage," 'minimal brain dysfunction,' hyperactivity, and attention deficit disorder or ADD. It was named ADHD in 1987.

Key Features
ADHD children have chronic difficulties with inattention, impulsivity and overactivity. These are the three key features of the disorder. It is obvious that these 'symptoms' are manifested by all children at some time. However in ADHD children they are considered to be inappropriate for their age or developmental level and they are displayed across a variety of situations. The behaviors are more severe and pervasive, and they persist.

Although it is typically diagnosed in young children, it should be noted that ADHD persists into adolescence and adulthood. Approximately 80% of children diagnosed in childhood continue to meet diagnostic criteria and to display symptoms as adolescents. Up to 70% of ADHD children will continue to have symptoms as adults. Thus ADHD is a chronic lifetime disorder. It has been linked with substance abuse and adverse effects on academic performance, vocational success and social and emotional development.

Diagnostic Criteria
The following diagnostic criteria were summarized from the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) or DSM-IV in an Australian Psychological Society Position Paper published in 1997.

 Symptoms of inattention (six or more, persisting for six months or more)
- failing to give close attention to details
- difficulty sustaining attention in tasks or play
- often not listening when spoken to
- often not following through on instructions and failure to finish
- difficulty organizing tasks and activities
- avoiding, disliking or reluctant to engage in tasks that require sustained mental effort
- often losing things necessary for tasks or activities
- easily distracted
- forgetful in everyday activities

 Symptoms of hyperactivity-impulsivity (six or more, persisting for six months or more)
- fidgets with hands or feet, squirms in seat
- leaves seat when remaining seated is expected
- runs about or climbs excessively and inappropriately
- difficulty playing or engaging in leisure activities
- often 'on the go'
- talks excessively
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or caused side effects. The authors suggested that the improvement in ADHD may be the result of improved sleep due to the amelioration of RLS/PLMS, or that ADHD and RLS/PLMS “may share a common dopaminergic deficit.”

Brain Imaging Studies

Studies have been done using structural imaging (computerized tomography (CT) and magnetic resonance imaging (MRI), functional imaging (positron emission tomography (PET) and single photon emission tomography (SPECT)) and both (functional magnetic resonance imaging (fMRI)).

CT studies

The early imaging studies used CT scans. A 1983 study compared CT scans in two groups of children, a cohort of ADD (sic) children and a control group, and could not differentiate between the groups. This led the authors to comment that, “if anatomic abnormalities are present in ADD (sic), they are not discernible using present-day CT technology.”

In 1986, young adults with a childhood history of ADHD showed a significantly greater frequency of cerebral atrophy than control subjects. However, all had been treated with stimulants in childhood and some also had a history of alcohol abuse.

In 1984 an emission CT study assessed regional cerebral blood flow (rCBF) in children with dysphasia and/or ADD, as it was then called, compared with control children (mainly siblings of those in the study group). Results showed that those with ADD had hypoperfusion in the white matter of the frontal lobes. In addition, most of the ADD subjects also showed hypoperfusion in the caudate nuclei region. A later study by the same group found the striatal regions to be hypoperfused. In both of these studies methylphenidate increased blood flow, leading the researchers to state that “methylphenidate medication tended to normalize the pathologic flow distribution in ADHD.”

It is interesting to note that a television report featured a study done on six hyperactive ADHD boys who were fidgety. On brain imaging they had reduced blood flow which returned to normal following the administration of Ritalin.

PET studies

A 1990 PET study investigated cerebral glucose metabolism in hyperactive adults with a history of hyperactivity since childhood compared with controls. Each subject in the patient group was a biologic parent of a hyperactive child. None had ever used stimulants, they had no history of substance abuse, and all had difficulty with restlessness and inattentiveness. It was found that “Glucose metabolism, both global and regional, was reduced in adults who had been hyperactive since childhood. The largest reductions were in the premotor cortex and the superior prefrontal cortex – areas earlier shown to be involved in the control of attention and motor activity.”

Other PET studies have been conducted to investigate cerebral glucose metabolism in ADHD adolescents and adults and have found a decrease in the metabolism of the basal ganglia.
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MRI studies (structural MRI)
Several of these have been conducted in the last ten years on children and adolescents. All have reported some differences between the ADHD and control groups regarding brain structures. Most findings have involved the basal ganglia.

One major study in 1996 compared 57 boys with ADHD with 55 healthy matched controls aged 5 to 18 years. The ADHD subjects had:
- smaller total cerebral volume
- loss of normal R>L asymmetry in the caudate
- smaller R globus pallidus, R anterior frontal region and cerebellum
- reversal of normal lateral ventricular asymmetry.

The authors concluded that their results are “consistent with hypothesized dysfunction of right-sided prefrontal-striatal systems in ADHD.”

Functional MRI (fMRI) studies
These have only recently been used to study ADHD. One early study of seven male ADHD adolescents and nine control subjects has shown “hypofrontality,” or less brain activity, during performance of certain tasks in the ADHD group. One of the tasks used was a ‘stop’ task, a task that requires response inhibition. The authors concluded that: “ADHD is associated with subnormal activation of the prefrontal systems responsible for higher-order motor control.”

A recent paper describes the use of a new fMRI technique. The study found that ADHD symptoms may be due to functional abnormalities of the putamen, which is an area that is mainly involved in the regulation of motor behavior.

SPECT studies
These have also only been introduced fairly recently into ADHD research. A 1995 study produced results which suggested abnormalities of blood flow and metabolism in the frontal lobe. In a 1997 project using SPECT to assess ADHD children and adolescents compared with a psychiatric control group, both at rest and doing a task, it was found that: 65% of the ADHD group revealed decreased perfusion in the prefrontal cortex with intellectual stress, compared to only 5% (sic) of the control group” and “of the ADHD group who did not show decreased perfusion, two thirds had markedly decreased activity in the prefrontal cortices at rest.”

The authors comment that “prefrontal lobe functions include attention span, concentration, judgment, activity level, critical thinking, and impulse control... With hypoperfusion in the prefrontal cortex there may be a loss of inhibition...resulting in hyperactive, impulsive, and inattentive behaviors.”

Genetic Studies
There is no evidence to suggest that ADHD is due to chromosomal abnormalities of structure, fragility or the presence of extra material but different lines of research strongly suggest that it is a highly hereditary condition.

Family aggregation studies
Between 10 to 35% of immediate family members of ADHD children are also likely to have ADHD, for siblings the figure is about 32%, and if a parent has ADHD the risk to offspring is 57%.

Adoption studies
Results show a strong possibility of significant hereditary contribution.

Twin studies
These support the notion that ADHD runs in families.

Molecular genetics
Some studies have been done attempting to find the gene/responsible. Studies on two dopamine sites (the dopamine transporter and the D4 receptor) have shown an association with ADHD.

Neuropsychology and Other Studies
A large number of studies have shown deficits on neuropsychological tests of frontal lobe functions. Results point to disinhibition of behavioral responses, difficulties with working memory, planning and other functions of the frontal lobe.

On continuous performance task (CPT) tests ADHD children make more errors than control children when performing tasks. The control children show increased frontal activation, especially in the right prefrontal region, on task performance. Children with ADHD show a lower level of such activation.

Differences between children with and without ADHD have been found on quantitative electroencephalography (QEEG) testing. Children with ADHD show elevated theta (slow wave) activity in the frontal regions.

Complications of Pregnancy and Birth
Some studies have found a slightly increased incidence of unusually short or long labor, fetal distress, low forceps delivery and eclampsia. In addition low birth weight, and birth injuries, have been associated with an increased risk of ADHD behaviors.

One study showed season of birth to be a risk factor, so it has been postulated that this is related to the incidence of seasonal viral infections. The authors concluded that “exposure to winter infections during the first trimester may account for some subtypes of ADHD.” They refer in particular to a statistically significant peak in September births for children with ADHD and comorbid learning disorders (Northern Hemisphere).

In the paper on striatal dysfunction that was mentioned earlier from 1989 it was noted by the researchers that retrospective pregnancy and birth data showed a high incidence of adverse antenatal and perinatal events. A more recent review paper by the leading researcher from that group discusses the continuation of their work regarding the vulnerability of the striatum if circulation is compromised, and the high incidence of ADHD in prematurity.

The authors of the 1996 imaging paper speculated that “an early, presumably fetal, event affecting normal development of asymmetry is etiologically related to ADHD.”

A 1999 paper in Pediatric Neurology looked at pre and perinatal striatal injury as a possible cause of ADHD and
found that "epidemiologic data suggest that perinatal adverse events may play a role in the pathogenesis of some cases of ADHD." 37

Finally, in a paper published in the Journal of Child Neurology looking at brain anomalies in ADHD children on MRI scan the authors concluded that early brain development could play a role in ADHD pathophysiology, and stated that: "the etiology of ADHD could be conceptualized as a genetically vulnerable brain that is subject to an environmental insult during early brain development and leading to aberrations in brain structure and function."

**Toxins**

**Lead**

Elevated body lead has been shown to have a "small but consistent and statistically significant relationship" to ADHD symptoms. 5

**Tobacco and alcohol (prenatal exposure)**

There is some relationship between prenatal exposure to tobacco and alcohol and inattention and hyperactivity, however lead it is currently only correlational. 9 There are confounding variables here. For example, does the woman who smokes in pregnancy and has an ADHD child have ADHD herself?

Barkley stresses that as with lead most studies on these substances have not been evaluated or controlled for the presence of ADHD in the parents. 4 However, there is one paper in which the authors found: "a strong and significant positive association between smoking by mothers during pregnancy and ADHD in their children that could not be attributed to socioeconomic status, parental ADHD and parental IQ."

**Diet**

**EFAs**

It has been proposed that at least some features of ADHD may reflect an abnormality of fatty acid metabolism. In a paper reviewing the literature to date, published in Prostaglandins, Leukotrienes and Essential Fatty Acids, the authors concluded that: "The consistent findings of both clinical signs of fatty acid deficiency and blood biochemical indices of fatty acid abnormalities in at least a subset of ADHD children indicate that supplementation with LC-PUFAs might be helpful in at least some cases."

The authors say that up to three months is needed for the benefits of such treatment to be seen, and also stress the need for further studies. However, they comment that fatty acids as a treatment are "relatively safe compared to existing pharmacological interventions."

**Zinc**

Zinc deficiency has been hypothesized as a cause of ADHD, however controlled studies are said to be lacking. 4 There has been some mention in the literature of a link between the EFAs and zinc, including in the above review of fatty acids.

An investigation into serum free fatty acids (FFA) and zinc has been carried out in ADHD children and controls. Results showed significantly lower levels for both FFA and zinc levels in the ADHD group. There was also a statistically significant correlation in the ADHD group, but not in the control group, between decreased FFA and zinc. 41

A study has been done to assess the relationship of zinc nutrition status to EFA supplementation and stimulant effects (dexamphetamine). In an 18 subject placebo-controlled double-blind crossover treatment comparison the subjects were classed as zinc-adequate, borderline, and deficient based on hair, red cell and urine zinc levels. Evening primrose oil (EPO) was only of benefit with borderline zinc levels. The researchers comment that their data suggest that zinc nutrition may be important for treatment of ADHD, and that if EPO benefits children with ADHD it probably does so by improving or compensating for borderline zinc nutrition. They conclude that further studies are needed. 42

**Magnesium**

One study on magnesium found a deficiency in 95% of a group of ADHD children. Levels were measured in hair, red blood cells and serum. 43 Another study by the same researchers cited elsewhere found that a cohort of ADHD children with magnesium deficiency showed behavioral improvement after six months of supplementation. 4

**Dairy, wheat, food additives, salicylates, sugar, yeast**

In a fairly recent review article about alternative treatments for ADHD published in Pediatric Clinics of North America the author concluded that: "Based on the research of the last 20 years, it is difficult to dismiss summarily the findings that a subgroup of children with ADHD responds favorably to individualized elimination diets."

**Poor Parenting**

Current thinking is that ADHD is influenced by the actions of the parents, but not caused by poor parenting. Parenting style/discipline methods used by these parents are now seen as a response to the child's behaviors. 44 The way in which parents parent ADHD children may exacerbate the ADHD behaviors, but it is not the cause of the disorder. Social factors alone are not considered to be causal of ADHD. 5

**Medical Drugs**

Pharmacological treatment is the most commonly used form of treatment, with 80% to 90% of ADHD children receiving medication. The main drugs used are the psychostimulants or stimulants, not sedatives as is sometimes incorrectly believed. Stimulant drugs were first used in the treatment of hyperactive children in 1937, 6 and Ritalin was first used in 1957, 44 so their use in treating such problems is not 'new.' Other relevant classes of drugs are the tricyclic antidepressants and the alpha adrenergic agonists. The newer antidepressants and major tranquilizers may also be used, depending on the child. 45

**Stimulants**

The stimulant drugs are so-called because they increase the level of arousal or alertness of the central nervous system. 6 The relevant drugs are two related but pharmacologically distinct drugs; methylphenidate (Ritalin) and dexamphetamine. Both enhance the activity of catecholamine neurotransmitters by increasing synaptic cleft concentration. The dopaminergic and noradrenergic neurons are facilitated and this: 46 "produces stimulation of the reticular activating system, limbic system, and prefrontal cortex, which are the..."
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areas of the central nervous system involved with attention, arousal, and inhibitory processes. It is generally considered that approximately 20% to 35% of ADHD children do not respond to these medications. There are many side effects of stimulants. They include insomnia, diminished appetite, weight loss, growth retardation, abdominal pain, headaches, impaired alertness, psychosis, nervousness, irritability, sadness and increased crying. They can also cause behavioral "rebound" at the end of the day, adverse cardiovascular and liver effects, and tics. In addition, desipramine is considered to have a high potential for drug abuse. The long term safety and efficacy of stimulants in children has not been well studied and little is known about their use in adolescence. Most studies on the stimulants have been short term despite the fact that long term treatment is considered to be indicated.

Tricyclic Antidepressants

Imipramine and desipramine are the most commonly used tricyclics. They are considered to be less effective than stimulants but of value for children with comorbid symptoms of anxiety or depression. Imipramine is preferred over desipramine because of a lower incidence of cardiovascular side effects although desipramine has been the best studied tricyclic for ADHD treatment. There have been cases of sudden death in children taking desipramine and one death occurred in a child on high doses of imipramine. Tricyclics are thought to present more risks than stimulants. Side effects of imipramine include impaired alertness, dry mouth, decreased appetite, nausea, insomnia, increased anxiety and adverse cardiovascular effects.

Alpha Adrenergic Agonists

Clonidine is an antihypertensive drug that is used in the treatment of ADHD, either alone or in combination with stimulants. It is considered useful for the control of aggressive behavior, and for counteracting some stimulant side effects such as sleep disturbance and lack of appetite. Side effects of clonidine include drowsiness, dry mouth, nausea, vomiting, depression and adverse cardiovascular effects (MIMS, 1999).

Of particular concern is the increase in the number of cases of clonidine overdose in children, a serious condition which requires treatment in an intensive care unit. The increased incidence of such overdose has been related to the increased use of this drug in children for treating ADHD. In addition there have been several reported cases of sudden death in children treated with clonidine and methylphenidate, so although that combination is used there is concern about its safety.

The newer antidepressants, moclobemide and fluoxetine (Prozac), have been studied in some ADHD children. Major tranquilizers, such as thioridazine, have also been used.

Controversy Over Medical Drugs

It has been said that no treatment in the whole fields of psychology, pediatrics or psychiatry has generated more controversy than the use of stimulants in treating ADHD. This is despite the fact that there have been many trials done on these drugs. As Lawrence Diller states in his book Running on Ritalin: "Over the past 35 years, ADD (sic) has been the most extensively studied pediatric psychiatric condition and Ritalin the most extensively studied psychotropic drug in pediatrics. Although the controversy continues, these drugs are widely prescribed. Concerns include the side effects, dependency and the possibility of leading to addictive behavior.

There are two other controversial issues: the use of psychotropic drugs in very young children, and the 'off label/ unlicensed' use of such drugs.

Two papers outlined the rise in the prescribing of psychotropics to preschoolers. In the JAMA paper it was found that the incidence of prescribing of psychotropics to preschoolers in the United States dramatically increased between 1991 and 1995. The other paper, which was published later in the year, expressed concern about such trends also occurring in Australia. Children aged as young as two are being prescribed stimulants. The authors state that there was: a 12-fold increase in the number of preschool children treated with stimulants between 1990 and 1999. There are no Australian data about the use of other psychotropic drugs in this age group, but our clinical experience shows that antidepressants, antipsychotics and clonidine are being used.

Given the concerns about the use of medical drugs to treat ADHD, what are the alternatives?

Alternative Treatments

Homeopathics

There are anecdotal claims of homeopathic treatment being of benefit. There is reference to one trial that showed improvement in the behavior of ADHD children. The children and caregivers, but not the investigator, were blinded regarding the treatment.

Phosphatidylserine (PS)

This is a phospholipid that has been trialled in the elderly for the treatment of dementia. It is available in over the counter products for ADHD in the United States. There is reference to two unpublished open pilot studies in children that found PS to improve attention, learning and behavior in 15 out of 20 children aged 4 to 19 years. It was also said to reinforce treatment already in place, such as Ritalin, so presumably the children had ADHD, but no further details were given. On further searching we found a paper by the same author that mentions an in-office physician study of 21 ADHD children aged 4 to 19 years that showed PS benefited over 90% of the children. The supplement was given for up to four months.

EFAs

Studies on EPO mentioned earlier suggest a limited role for essential fatty acids. There is a patented product available which is produced for ADHD treatment. It contains evening primrose oil, tuna oil, vitamin E and thyme oil. The thyme oil has been included as an antioxidant. It appears that no studies have been published in peer-reviewed journals on this combination.

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Ginkgo and Ginseng

Ginkgo is often present in herbal remedies for ADHD although reports of benefit are said to be anecdotal. A recent survey found that its use in ADHD was relatively high. A combination of Ginkgo standardized extract and American ginseng (Panax quinquefolium) was tested for its ability to improve ADHD symptoms in a pilot clinical trial. Results were suggestive of a positive effect, but the trial was hampered by poor elements of design such as the fact that assessment was only by parents and the trial was not blinded, had no control group and was of short duration (4 weeks).

A combination of Ginkgo and Korean ginseng (Panax ginseng) significantly enhanced mental performance in healthy volunteers, which suggests that it might be of benefit in ADHD. College students were tested four times between one and six hours after taking the herbs. Those receiving Ginkgo only demonstrated significantly improved concentration within 2.5 hours. The highest dose tested (360 mg of 50:1 standardized extract) was the most effective. A dose of 400 mg of 5:1 Korean ginseng extract (equivalent to 2 g of root) sharpened memory after just one hour, with improvements in ability to store, hold and retrieve information.

But when both the Ginkgo extract (360 mg equivalent to 18 g of leaf) and the Korean ginseng extract (600 mg, equivalent to 3 g of root) were combined as a single treatment, the results were remarkable. Not only was the effect on cognitive function more pronounced than treatment with either herb on its own, it was immediately evident when the volunteers were first tested. The lead researcher, Dr Andrew Scholey was quoted as saying: "The results were incredible in terms of improvements in speed and accuracy – usually there is a trade-off and you improve one at the expense of the other."

Bacopa

In a survey of herbal practitioner prescribing patterns, 31% of Australian practitioners nominated Bacopa as their first choice for treating ADHD. The preference for Bacopa is explained by its beneficial effects on concentration and information processing, especially from the study in children. Bacopa had a positive effect on concentration, but not on short-term memory, in a small number of volunteers tested in the mid-1960s. Bacopa (1 g/day for 3 months) improved intellectual functions such as visual motor function, short-term memory and mental reaction times in children. Unlike those treated with Bacopa, the placebo group did not improve from baseline values.

An Australian clinical trial examined the long-term effects of a Bacopa extract on cognitive function in 46 healthy human volunteers. The study was of double-blind, placebo-controlled design in which subjects were randomly allocated to receive Bacopa or placebo. Neuropsychological testing was conducted before treatment and at 5 and 12 weeks after treatment. After 12 weeks the largest cognitive change from Bacopa treatment (which was also statistically significant compared to placebo, p<0.05) was a time reduction for the Inspection Time (IT) test (64.5 ± 16.7 min vs 75.9 ± 25.3 min).

IT is regarded as a measure of the integrity of the early stages of information processing and may act as a rate-limiting factor for cognition. This indicates that Bacopa significantly improved the speed of visual information processing. Verbal learning rate and memory consolidation as assessed by the Rey Auditory Verbal Learning Test were also somewhat improved against placebo at 12 weeks (p<0.05). But the most striking finding was the highly significant (p=0.001) reduction in anxiety in volunteers receiving Bacopa. The percentage of adverse effects was similar for both groups, except that there was a higher incidence of nausea, dry mouth and fatigue in the Bacopa group.

Valerian

Clinical trials of a valerian proprietary product have been conducted in children but not specifically for ADHD. Research has shown valerian to be beneficial for the treatment of sleep problems in ADHD children, and this has also led to improvement in daytime behavior.

Pine Bark Extract

A study which compared pine bark extract with Ritalin or placebo in 24 adults with ADHD under a double-blind crossover design found that neither the herbal extract nor the drug outperformed the placebo control. The conservative dosage levels and relatively brief length of treatment could have contributed to the lack of significant findings.

Conclusions

ADHD is a complex, multifactorial disorder involving, among other factors, abnormalities in cerebral blood flow, CNS metabolism and neurotransmitter levels. A number of herbs such as Ginkgo, Korean or American ginseng, Bacopa and valerian could theoretically provide benefit in correcting some of those abnormalities, but at present their use in ADHD is speculative.

The way forward is to conduct well-designed trials involving carefully selected phytotherapeutic treatments for children suffering from ADHD. Desperate parents need a credible alternative to the widely-used, but potentially damaging, conventional drugs which are currently prescribed.

Acknowledgments

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